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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/501,039	KOKUBO ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-10 have been canceled. Claims 11-14 have been added and are under consideration.

Applicant's arguments filed 8-10-07 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 101

Claims 11 and 13 are rejected under 35 U.S.C. 101 because the claimed invention encompasses non-statutory subject matter for reasons of record. Claims 11 and 13 encompass introducing a plasmid into an animal host cell in vivo and selecting a transformant that is a human. As such, the claims still encompass selecting a transgenic human. The claims are not limited to isolating cells from the animal and selecting a transformant from the cells in culture or to injecting a plasmid encoding PPK operably linked to a target gene promoter into an animal (i.e. gene therapy) and monitoring activity of the promoter in vivo. Selecting transformants that are genetically altered humans is non-statutory subject matter.

Claim Rejections - 35 USC § 112

New Matter

Claims 11-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection regarding the breadth of "target gene" has been withdrawn in view of pg 9, paragraph 2.

However, the phrase "monitoring expression of a target gene" in claims 11-14 does not have support in the specification to its full breadth. Pg 12, for example, is limited to monitoring the activity of the target gene promoter (GAL1 promoter) (last sentence of first paragraph) and not expression of the target gene product (GAL1). The examples are limited to monitoring the activity of a target gene's promoter by linking it to PHM4.

The phrase "yeast whose PHM4 gene is knocked out" in claims 12 and 14 is readily apparent from the phm4 knockout yeast cell line described on pg 11, lines 8-10, and pg 12, lines 1-2.

The step of "preparing a plasmid in which a polyphosphate kinase (PPK) gene is connected in frame and downstream of the target gene" in claims 11 and 13, step a) remains new matter. Applicants point to "previously presented claims"; however, applicants must point to originally filed claims or citations in the specification originally filed. Applicants point to pg 8, last paragraph, pg 9, last paragraph, and pg 12, paragraph 1, none of which describe the connection claimed. Pg 12, lines 1-12, for example, is limited to a plasmid encoding PHM4 gene downstream from the GAL1 promoter. The claims should be limited to a plasmid encoding PPK in frame and downstream of the target gene promoter.

Likewise, the step of "preparing a plasmid in which a polyphosphate kinase (PPK) gene or PHM4 gene is connected in frame and downstream of the target gene" in claims 12 and 14, step a) remains new matter. Pg 8, last paragraph, pg 9, last paragraph, and pg 12, paragraph 1, do not describe the connection claimed. The claims should be limited to a plasmid encoding PPK or PHM4 in frame and downstream of the target gene promoter.

The step of "introducing the plasmid into an animal host cell" in step b of claims 11 and 13 remains new matter. Applicants point to pg 12, first paragraph, which is limited to introducing a plasmid encoding PHM4 operably linked to the target gene (GAL1) promoter into a yeast cell line. Applicants argue techniques for introducing plasmids into animal cells were well established at the time of filing. Applicants' argument is not persuasive because it is not readily apparent the specification contemplates introducing the plasmid into animal cells.

Culturing selected transformants and inducing expression of PPK in animal host cells, step c) of claims 11 and 13, remains new matter. The last paragraph of pg 11 and the first paragraph of pg 12 pointed to by applicants are limited to yeast cells. Applicants' arguments are limited to inducing PPK expression in yeast cells.

The step of "inducing expression of the PPK gene or the PHM4 gene" in step c of claims 12 and 14 remains new matter. Support cannot be found for inducing a PPK gene in yeast. Paragraph 1 on pg 12 is limited to inducing PHM4 expression; however, it is not clear what substrate induced PHM4 expression. Therefore, it is not readily apparent that applicants taught how to induce expression of PHM4 or PPK as claimed.

The step of quantifying in step d of claims 11 and 13 remains new matter. Pg 7 and 9-12 are limited to yeast cells. In particular, pg 8 states:

> "As mentioned above, polyphosphate can accumulate in all organisms in significant amounts and can be quantified directly by 31P-NMR. Polyphosphate synthetase genes, for instance PHM genes of Saccharomyces cerevisiae, specifically PHM 1-4 genes placed downstream of the chosen gene and in-frame with it allow transcription to be quantified in real time. The polyphosphate generated by this method has a mean length of up to 50 phosphate groups, within the detectable range by NMR. The 10 mer is thought to show the highest sensitivity for 31P-NMR. The polymer sizes can be confirmed by staining the cell contents with toluidine blue after polyacrylamide gel-electrophoresls. Importantly, NMR signals derived from polyphosphate can be independently quantified without interference from signals of nucleic acids. DNA sequences of PHM 1-5 genes and amino acid sequences of PHM 1-5 are shown by Seq. I.D. Nos. 1-10. As for the polyphosphate synthetases used, there is no particular restriction as long as the synthetases can generate polyphosphate intracellularly. PPK (polyphosphate kinase) derived from prokaryotic organisms, functional homologues, or orthlogues, other than PHM of the aforementioned Saccharomyces cerevisiae can be used."

The specification does not teach quantifying polyphosphate in animal cells as claimed.

The limitation of "having a strand length equal to or less than 50 mer" in step d of claims 12 and 14 remains new matter. Pg 7, pg 9-12 and Fig. 1-4 do not disclose quantifying accumulation of polyphosphate "having a strand length equal to or less than 50.mer." No such limit is readily apparent.

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of using yeast cells to monitor the

activity of a target gene promoter comprising: (a) preparing a plasmid in which a PHM4 gene is connected in-frame and downstream of a GAL1 promoter; (b) introducing the plasmid into yeast cells in which the PHM4 gene is knocked out; (c) selecting a transformant; (d) culturing the selected transformant; (e) inducing expression of the PHM4 gene by administering a substrate of GAL1; (f) quantifying accumulation of polyphosphate in the selected transformant and in a cultured non-transformant by one-dimensional 31P-NMR and/or 1H-NMR imaging; and (g) comparing the accumulation of polyphosphate in the transformant to the non- transformant, wherein an increase in polyphosphate in the transformant compared to the non-transformant indicates activity of the target gene promoter, does not reasonably provide enablement for the claims as broadly written, specifically for visualizing gene expression in animal cells in vivo using the method claimed and described on pg 4, lines 2-3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 11 and 13 are directed to monitoring expression of a target gene in animal cells. The claims encompass visualizing gene expression in animal cells in vivo because the "transformants" are not in vitro, because transformants can be multicellular animals and because pg 3, line 20, through pg 4, line 12, states one purpose of the method claimed is to visualize gene expression in animals in vivo. The examples are limited to monitoring promoter activity in yeast cells having a deletion of the PHM4 gene and using the PHM4 gene as a reporter gene in the plasmid operably linked to the target gene promoter. The specification does not teach how to quantify accumulation of

polyphosphate in animal cells, specifically in an animal in vivo. In particular, pg 8 states:

> "As mentioned above, polyphosphate can accumulate in all organisms in significant amounts and can be quantified directly by 31P-NMR. Polyphosphate synthetase genes, for instance PHM genes of Saccharomyces cerevisiae, specifically PHM 1-4 genes placed downstream of the chosen gene and in-frame with it allow transcription to be quantified in real time. The polyphosphate generated by this method has a mean length of up to 50 phosphate groups, within the detectable range by NMR. The 10 mer is thought to show the highest sensitivity for 31P-NMR. The polymer sizes can be confirmed by staining the cell contents with toluidine blue after polyacrylamide gel-electrophoresls. Importantly, NMR signals derived from polyphosphate can be independently quantified without interference from signals of nucleic acids. DNA sequences of PHM 1-5 genes and amino acid sequences of PHM 1-5 are shown by Seq. I.D. Nos. 1-10. As for the polyphosphate synthetases used, there is no particular restriction as long as the synthetases can generate polyphosphate intracellularly. PPK (polyphosphate kinase) derived from prokaryotic organisms, functional homologues, or orthlogues, other than PHM of the aforementioned Saccharomyces cerevisiae can be used."

The specification does not teach how to quantify polyphosphate in animal cells in vitro or in vivo. The specification does not correlate quantifying polyphosphate in yeast cells to animal cells in vitro or in vivo. It is not readily apparent that quantification of polyphosphate in yeast and animal cells are performed the same way or that methods of quantifying polyphosphate in animal cells in vitro or in vivo were known at the time of filing. Without such guidance, it would have required those of skill undue experimentation to perform the method claimed in animal cells.

Claims 11 and 13 encompass performing the method in animal cells that do not have a knocked out PPK gene; however, expression of the plasmid PPK gene in a yeast or animal cell would be clouded by endogenous expression of PPK. Thus, knocking out the PPK gene appears essential to the invention in either yeast or animal

cells. However, the specification does not teach how to knock out any PPK genes in animal cells. If the method can be performed without knocking out the PPK gene, please point to where such a method is disclosed in the specification originally filed. Without such guidance, it would have required those of skill undue experimentation to perform the method in animal cells either in vitro or in vivo.

Claims 11-14 encompass monitoring expression of a target gene of the cell. However, the target gene is actually in part of the plasmid. This should be clarified in the preamble of the claims.

The specification does not enable monitoring expression of a target gene as broadly claimed (claims 11-14). The "expression" actually being monitored is the activity of the target gene's promoter (pg 12, first paragraph). The method does not monitor activity of a promoter endogenous to the cell and does not monitor expression of the target gene product. For example, the method described on pg 12 is incapable of monitoring the amount of GAL1 expressed because the plasmid does not encode GAL1. The specification does not provide adequate guidance to correlate monitoring target gene promoter activity to monitoring gene expression as broadly claimed. Overall, it would have required those of skill undue experimentation to determine how to perform the method as broadly claimed.

The specification does not enable "inducing expression of the PPK gene" "or the PHM4 gene" as broadly claimed (claims 11-14). Pg 12, first paragraph, appears to be limited to inducing the GAL1 promoter using one of the compounds; however, it is not

readily apparent which compound induces the GAL1 promoter because the description is incomplete. Pg 12, lines 3-6, states:

> "After transformants were selected on a minimal synthetic medium, they were grown in YPG medium (Bacto yeast extract [1% w/v], Bacto peptone [2% w/v] and galactose [2% w/v]), and the expression of PHM4 genes was induced."

Inducing expression of the PPK gene is a misnomer. The target gene promoter (GAL1) is actually being induced using a substrate. The specification does not teach which is the substrate that induces the GAL1 promoter or other substrates that induce other target gene promoters so that PPK or PHM4 is expressed. Without such guidance, it would have required those of skill undue experimentation to induce PPK or PHM4 expression using any target gene other than GAL1.

Quantifying polyphosphate "having a strand length equal to or less than 50 mer" is not enabled in the specification. No such limitation is readily apparent from pg 9-12 or Fig. 1-4. Accordingly, it would have required those of skill undue experimentation to quantify such polyphosphates.

Indefiniteness

Claims 11-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11-14 require monitoring expression "of a target gene in a cell" in the preamble, but the body of the claim requires the plasmid encodes the target gene. While the plasmid is introduced into the cell, the target gene is in a plasmid not in a cell.

The preamble does not have a proper nexus with the body of the claim. The preamble should be limited to using a cell to monitor or determine

Claims 11-14 require monitoring expression of a target gene, but the method actually requires determining activity of the promoter of a target gene. Expression of PPK or PHM4 is monitored – not expression of the target gene as claimed.

Claims 11-14 are indefinite because the phrase "quantifying accumulation of polyphosphate having a strand length equal to or less than 50 mer" remains indefinite. It appears that the phrase is intended to limit which polyphosphates are being quantified; however, the metes and bounds of the polyphosphates being quantified cannot be determined. It cannot be determined how to distinguish PPK made by the transformant after expression has been induced vs. endogenous PPK made by the transformant before expression is induced. More particularly, it cannot be determined how to distinguish polyphosphates having a mean value strand length equal or less than 50 mer from those that do not. Pg 8 teaches quantifying transcription of PHM1-4 by 31P-NMR. Pg 8 states "The polyphosphate generated by this method has a mean length of up to 50 phosphate groups, within the detectable range by NMR."

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims allowed

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

/Michael C. Wilson/
Patent Examiner